REMARKS

Claim 29 has been amended. Support for this amendment may be found at least on pg. 4, line 17 to pg. 5, line 30 of the specification, and original claims 1, 5 and 6. Claims 32 and 33 have been amended to correct indefiniteness. Specifically, Applicant has amended claim 32 to recite a range "from 0.5 to 30 million" and claim 33 to recite "tumor is less than 0.5 cm." Support may be found at least on pg. 12, lines 9-10 of the specification. Claim 33 finds support on pg. 12, lines 23-26 of the specification. Claims 40-44 have been cancelled. No new matter has been added. Claims 29-35 are now pending in the application.

Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections in view of the following remarks and the attached declaration under 37 C.F.R. § 1.132.

Rejections under 35 U.S.C § 112, second paragraph

Claims 29-35 and 40, 41, 43 and 44 stand rejected under 35 U.S.C § 112, second paragraph. In order to expedite prosecution and without acquiescing in the rejection, Applicant has amended Claim 29 to further point out the invention being claimed. Amended Claim 29 finds support in pg 4, line 17 to pg. 5, line 30 of the specification. However, Applicant respectfully maintains that it is not necessary to provide a step for distinguishing the primary stimulated PBMC from the added naïve PBMC, because CAPRI cells are defined on pg. 16, line 8 of the specification as "naïve PBMC imprinted with activated PBMC."

Furthermore, Claims 32 and 33 have been amended. Claim 32 has been amended to recite "range from ~~about~~ 0.5 to ~~about~~ 30 million" and claim 33 to recite "tumor is ~~about~~ less than 0.5 cm ~~or less~~." Claims 40, 41, 43 and 44 are cancelled without prejudice or disclaimer.

Applicant respectfully requests that the rejections of pending independent claim 29 and dependent claims 30-35 under 35 U.S.C § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C § 112, first paragraph

Claims 29-35 and 40, 41, 43 and 44 stand rejected under 35 U.S.C § 112, first paragraph, as purportedly reciting new matter. Without acquiescing in the rejection, Applicant has removed the subject matter cited by the Office. Specifically, Applicant has amended claim 29 to remove the new matter cited by the examiner, and cancelled claims 40, 41, 43 and 44. Accordingly, it is respectfully requested that the rejections of pending independent claim 29 and dependent claims 30-35 under 35 U.S.C § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C § 103(a)

Claims 29-32, 34, 35, 40, 41, 43 and 44 stand rejected under 35 U.S.C. 103(a) as purportedly obvious over *Babbitt et al.* (5,766,920) in view of *Gold et al.* (J Surg Red. 1995 Aug;59(2):279-86), *Rudolf Wank* (WO 99/50393) and *Marzo et al.* (J Immunol. 1999 May 15;162(10):5838-45). Claims 40-44 have been cancelled without prejudice or disclaimer. The rejections of remaining Claims 29-32, 34, and 35 under 35 U.S.C. 103(a) are respectfully traversed.

The Office cites Babbitt as purportedly teaching a method for treating cancer, wherein the method comprises (a) obtaining peripheral-blood mononuclear cells (PBMC) from a cancer patient, (b) exposing said PBMC to anti-CD3 antibodies and IL-2, (c) removing the cell culture supernatant (referred to as "T3CS" by Babbitt) and measuring the levels of IL-2

and anti-CD3 antibodies in the cell culture supernatant, (d) obtaining a second population of peripheral-blood mononuclear cells (PBMC) from the same cancer patient, (e) exposing said second population of PBMC to the T3CS cell culture supernatant including supplemental addition of anti-CD3 antibodies and IL-2 if so desired and (f) administration of the second population of PBMC cells to the cancer patient.

However, the process of activation in *Babbitt et al.* is substantially distinct from that of the present invention wherein the CD3-activated PBMCs themselves, and not a supernatant from CD3-activated PBMCs, are used to stimulate naïve PBMC. More specifically, the present invention discloses that optimal activation of naïve T cells requires a specific antigenic stimulation of the αβ T cell receptor (αβ TCR) (pg. 1, lines 13-20; pg. 8, line 30 – pg. 9, line 2; pg. 10, lines 2-8). The activation of T cells via the αβ TCR leads the T cells to differentiate into (MHC-restricted) effector T cells (pg. 10, lines 2-8).

Activation with immobilized anti-CD3 antibodies causes internalization of both CD3 and αβ TCR of the T cells (see abstract and pg. 4, lines 3-6 of the Wank manuscript included with the attached 37 C.F.R. § 1.132 declaration of Dr. Wank; Alcover, A. & Alarcon, B., Internalization and intracellular fate of TCR-CD3 complexes, Crit. Rev. Immunol. 20, 325-346 (2000))). In the course of stimulation via cascade priming in accordance with the present invention, the first PBMC population is activated with immobilized anti-CD3 antibodies, becoming the primary stimulated PBMC with internalized CD3 chains and internalized αβ TCR. Therefore, the primary stimulated PBMC can no longer be differentiated into effector cells, such as cytotoxic T cells. However, the T cells of the primary stimulated PBMC do produce cytokines, which results in stimulation of the antigen-presenting cells (APC) (pg. 9, lines 21-30). Once the primary stimulated PBMC are incubated with naïve PBMC, the stimulated APC present immunogenic cancer peptides to the αβ TCR of the non-stimulated T

cells in the naïve PBMC (pg. 1, lines 10-27, pg. 10, lines 1-8). This αβ TCR stimulation results in differentiation of the non-stimulated (naïve) T cells into cytotoxic (killer) and helper effector T cells (pg. 8, line 30 – pg. 9, line 2; pg. 10, lines 2-8), which kill cancer cells. The T cells from the primary stimulated PBMC are not active on the cancer cells because they have their αβ TCR internalized and, thus, cannot develop into cytotoxic or effector cells, as illustrated in Figure 1 of the enclosed 37 C.F.R. § 1.132 declaration and manuscript.

In contrast, *Babbitt et al.* discloses non-specific activation of the T cell with CD3 antibodies and the cytokines generated during activation, and does not disclose activation of the αβ TCR to produce cytotoxic T cells (see col. 3, lines 12-17: "the immunoreactive cells… which have been generated independent of disease-specific antigens utilizing a mixture of non-specific activators, i.e. autologous cytokines and a mouse monoclonal antibody, i.e. OKT3, as a synergistic antibody"). Although *Babbitt et al.* induces the proliferation of T cells (Figures 2-6), it does not induce activation of the cytotoxic mechanism via the decisive αβ TCR. The binding of OKT3 to T lymphocyte in *Babbitt et al.* results in their early activation, which leads to cytokine release, followed by the blocking of T cell functions, including internalization of the αβ TCR (see the Alcover & Alarcon reference cited above). Moreover, following the depletion of OKT3 in *Babbit et al.* there was little or no measurable activation of T cells, "i.e. the autologous cytokines were not capable of stimulating resting PBMC in the absence of OKT3" (col. 13, lines 55-58). The present invention, however, uses the primary stimulated PBMC to stimulate the naïve PBMC and no supplemental stimulating agents are required (pg. 4, lines 9-24). Therefore, while *Babbitt et al.* discloses activation of T cells via CD3-induction to stimulate cytokine release, it does not disclose the subsequent cytokine-induced activation of APC nor the activation of the T cells included in the naïve PBMCs into cytotoxic effector T cells via a specific interaction of the MHC/cancer peptide

complex of the activated APCs with the αβ TCR of the naïve T cells. Thus, the T cell activation mechanism of the present invention is non-obvious over and distinct from the non-specific activation mechanism in *Babbitt et al.* As such, one skilled in the art would not look to *Babbitt et al.* for motivation when seeking means to produce cytotoxic cells, specifically through activation of the αβ TCR, for the treatment of cancer.

In parallel, *Gold et al.* discloses that the underlying mechanism of a specific anti-tumour response generated via non-specific *ex vivo* activation with T3CS is not clear as it was shown that T3CS expands only the number of memory T cells and obviously NK cells, "but not the naïve T cell subset in patients" (pg. 284, last paragraph). Therefore, one skilled in the art looking for a method to treat cancer by activating naïve T cell subsets would not look to *Gold et al.* for motivation.

In view of the foregoing arguments, because the method in *Babbitt et al.* results in an internalization of both CD3 and αβ TCR, which would prohibit the activation of naïve PBMC T cells via the αβ TCR, one skilled in the art would not look to *Babbitt et al.* for motivation to produce effector T cells via αβ TCR stimulation. One skilled in the art looking to utilize effector T cells would also not combine *Babbitt et al.* or *Gold et al.* with *Wank* because the use of the T3CS supernatant of *Babbitt et al.* which contains the OKT3 antibody would also result in an internalization of both CD3 and αβ TCR, thereby prohibiting the production of the effector T cells taught in *Wank.* Similarly, *Marzo* in fact supports the non-obviousness of the present invention because *Marzo* emphasizes the importance of employing cytotoxic T cells for effective tumor eradication, the production of which would be prohibited using the method of *Babbitt et al.* (*Marzo*, pg. 5844, right col.).

Furthermore, while CD3-activated PBMC, as disclosed in *Babbitt et al.,* and *Gold et al.,* show at most a minimal autologous cancer cell lysis, the method for treating cancer with

CAPRI cells according to the present invention surprisingly was found to kill autologous cancer cells directly and efficiently within 18-24 hours, as disclosed in the supporting 37 C.F.R. § 1.132 declaration (see Figure 1).

Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness (MPEP 716.02(a)). No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 See also *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria). As shown in the attached Figure 1, the method according to the present invention for treating cancer using CAPRI cells was surprisingly found to be far superior to the method of using CD3-activated PBMC to achieve cancer cell lysis as disclosed in *Babbitt et al.,* and *Gold et al.* More specifically, a nearly complete lysis of autologous cancer cells by CAPRI cells was observed, while the CD3-activated PBMC showed no significant lytic activity (see attached Figure 1). Therefore, the method for treating cancer according to the claimed invention is non-obvious over the prior art.

Figure 1 also supports the arguments outlined above, such that the method in *Babbitt et al.,* does not produce cytotoxic effector cells via stimulation of the αβ TCR. Specifically, the contrast between the results shown in Figure 7 of *Babbitt et al.,* and the results disclosed in Figure 1 of the 37 C.F.R. § 1.132 declaration and manuscript of Dr. Wank, can be explained by the susceptibility of the K526 leukemia cell line and allogeneic renal carcinoma cell line 769P to natural killer (NK) cells. As known in the art, the K526 and 769P cancer cell lines show no or only a minimal expression of MHC (HLA) antigens (see, e.g.,

Kronenberg, M., Toward an understanding of NKT cell biology: progess and paradoxes, Ann. Rev. Immunol. 23:877-900 (2005)). Such cells that have aberrant MHC expression are killed by NK cells (see the attached page 363 of the immunology textbook "Kuby Immunology" (6th ed., 2006, W.H. Freeman and Company). Therefore, the NK cells, which would be present in *Babbitt et al.*'s PBMC and would be activated by the cytokines secreted from the PBMC, would destroy the cancer cell lines K526 and 769P (Figure 7). However, NK cells are inactivated by autologous HLA class I molecules, which are expressed by most cancer cells. Therefore, if the NK cells were responsible for the results obtained by *Babbitt et al.* in Figure 7, it would explain the poor lyzing performance of the CD3-activated PBMC against autologous breast cancer cells shown in Figure 1 of the attached manuscript and 37 C.F.R. § 1.132 declaration, and further support the non-obviousness of the claimed invention.

In view of the foregoing arguments, Applicant respectfully requests that the rejections of pending independent claim 29 and dependent claims 30-32, 34 and 35 under 35 U.S.C § 103(a) over *Babbitt et al.*, in view of *Gold et al.*, *Rudolf Wank*, and *Marzo et al.*, be withdrawn.

Claims 29 and 33 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over *Babbitt et al.* (5,766,920) in view of *Gold et al.* (J Surg Red. 1995 Aug;59(2):279-86), *Rudolf Wank* (WO 99/50393) and *Marzo et al.* (J Immunol. 1999 May 15;162(10):5838-45), *Gale Granger* (5,837,233) and *Johnson et al.* (5,217,704). Primarily, for the reasons stated above, one skilled in the art would not combine *Babbitt et al.* and *Gold et al.* with *Wank*, especially in view of *Marzo et al.*. Moreover, there are further superior results achieved according to the method of treating cancer claimed in the present invention that render it non-obvious over *Granger* and *Johnson et al.*

Specifically, the Examiner cites *Granger* to support the treatment of tumors by incubating PBMCs obtained from the cancer patient with allogenic doner PBMCs *ex vivo* and then administering the cells directly into the tumor. *Granger* teaches that cytokine production directly within a tumour can induce tumour regression (col. 1-3). In contrast, as highlighted above, the present invention induces tumour regression through the production of cytotoxic effector T cells. Therefore, one skilled in the art would not look to *Granger* for motivation.

The method according to the present invention produces generates cytotoxic effector T cells which lyse cancer cells in a MHC-restriced manner, as illustrated in Figure 2 of the attached manuscript and 37 C.F.R. § 1.132 declaration. Furthermore, the present invention results in the maturation of freshly added $CD14^+$ monocytes that are included in the naïve PBMC into $CD83^+$ dendritic cells, as illustrated in attached Figure 4 of the manuscript and declaration, which is a superior, unexpected result to the disclosures and teachings of *Granger* and *Johnson.* $CD83^+$ dendritic cells are antigen-presenting cells (APCs) which present tumour-immunogenic peptides in a particularly effective manner and are therefore important in the preparation of CAPRI cells according to the present invention. Furthermore, the CAPRI cells of the present invention surprisingly enhance the HLA class I and HLA class II surface expression in epithelial and other solid malignant tumor cells to enhance the expression of immunogenic tumor peptides, which is a deciding factor of the high cytotoxic capacity of CAPRI cells against various cancer cells (see attached Figure 3). These results obtained according to the presently claimed method of treating cancer are superior and unexpected over the disclosures and teachings of *Granger* and *Johnson,* which further supports the non-obviousness of the present invention. Therefore, Applicant respectfully requests that the rejections of pending independent claim 29 and dependent claim 33 under

U.S.C. § 103(a) as being unpatentable over *Babbitt et al.,* in view of *Gold et al.*, *Rudolf Wank, Marzo et al.*, *Gale Granger*, and *Johnson et al.* be withdrawn.

In view of the foregoing amendments and remarks, Applicant respectfully submit that the application is in condition for allowance. Applicant respectfully request favourable consideration and prompt allowance of the application.

Conclusion

If there are any questions regarding this response or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket # 104341.B090019).

Respectfully submitted,

June 17, 2009

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